IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Shinichi YASUEDA et al.

Serial No.: 09/529,882 Group Art Unit: 1615

Filed: April 21, 2000 Examiner: C. L. EVANS

For: AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION

DECLARATION UNDER RULE 1.132

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

I, Katsuhiro INADA, citizen of Japan and residing in Kobe-shi, Hyogo-ken, Japan declare and say that:

1. I am a graduate of the Master Course in Pharmacy of the Graduate School of Kinki University, Japan in March, 1989.

2. Since April, 1989 up to this time, I have been an employee of Senju Pharmaceutical Co., Ltd., and have been engaged in the research and development of pharmaceutical preparations.

3. At present, I am a member of the Pharmaceutical Society of Japan.

4. I am familiar with the subject matter of the above-identified application.

5. I have read the Office Action mailed March 26, 2001 and the reference (U.S. Patent 4,780,465) cited therein and am familiar with the subject matter thereof.

6. In order to show unexpected effects of the invention claimed in the above-identified application, the following experiments have been done under my direction.

In the following expreiments, the compound disclosed in the reference, 1-ethyl-6,8-difluoro-1,4-dihydro-7-(3-methyl-1-piperazinyl)-4-oxoquinoline-3-carboxylic acid, is referred to as Compound I.

Experiment 1

Effect of disodium edetate on preventing coloration of Compound I

Method

According to the following formulations G and H, aqueous liquid preparations of Compound I were prepared in stainless steel (SUS316) beakers, respectively. Concentrated glycerin was formulated as an isotonizing agent in both formulations. Disodium edetate was formulated in the formulation G but not formulated in the formulation H. Coloration of Compound I in these formulations was observed by visual assessment.

Formulations	G	H
Compound I	0.3 g	0.3 g
Concentrated glycerin	2.4 g	2.4 g
Disodium edetate	0.01 g	-
Benzalkonium chloride	0.002 g	0.002 g
Sodium hydroxide	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml
pH	6.0	6.0

Results

In both formulations G and H, the appearance showed colorless, clear solution immediately after preparation.

This result shows that coloration of Compound I does not depend on the presence of disodium edetate in the preparation or not.

Experiment 2

Effect of disodium edetate on precipitation of Compound I crystals

Method

According to the following formulations E and F, aqueous liquid preparations of Compound I were prepared. Sodium chloride as an isotonizing agent and disodium edetate as a chelating agent were formulated in the formulation E. In the formulation F, concentrated glycerin as an isotonizing agent was formulated but not disodium edetate. These formulations were subjected to freezing at -30°C (overnight) and then thawing at room temperature to observe precipitationof Compound I crystals.

Formulations	E	F
Compound I	0.3 g	0.3 g
Concentrated glycerin	-	2.4 g
Sodium chloride	0.9 g	-
Disodium edetate	0.05 g	-
Benzalkonium chloride	0.002 g	0.002 g
Sodium hydroxide	q.s.	q.s.
Sterilized purified water	to total	to total

	100 ml	100 ml
pH	6.0	6.0

Results

Just after preparation, both formulations E and F showed clear solution. After subjected to freezing and thawing once, crystals were precipitated in the formulation E but no precipitation of crystals was recognized in Formulation F.

These results show that precipitation of Compound I crystals under storage conditions at a low temperature is prevented by formulating concentrated glycerin in an aqueous liquid preparation of Compound I but not prevented by formulating disodium edetate.

Experiment 3

Effect of chelating agents on precipitation of Gatifloxacin crystals

Method

According to the formulations J, K, and L, aqueous liquid preparations of Gatifloxacin were prepared. These formulations were subjected to freezing at -30°C (overnight) and then thawing at room temperature repeatedly to observe precipitation of Gatifloxacin crystals.

Formulations	J	K	L
Gatifloxacin	0.5 g	0.5 g	0.5 g
Disodium edetate	0.05 g	-	-
Sodium citrate	-	0.05 g	-
Condensed sodium phosphate	-	-	0.05 g

Sodium chloride	0.9 g	0.9 g	0.9 g
Benzalkonium chloride	0.002 g	0.002 g	0.002 g
Hydrochloric acid	q.s.	q.s.	q.s.
Sodium hydroxide	q.s.	q.s.	q.s.
Sterilized purified water	to total 100 ml	to total 100 ml	to total 100 ml
pH	6.0	6.0	6.0

Results

In the formulation in which condensed sodium phosphate was formulated as a chelating agent (formulation L), crystals were precipitated during preparing the aqueous liquid preparation. For formulation K in which sodium citrate was formulated, crystals were precipitated when freezing and thawing were repeated twice to three times. On the other hand, when disodium edetate was formulated (formulation J), no precipitation of crystals was recognized even when freezing and thawing were repeated ten times.

These results show that precipitation of Gatifloxacin crystals under storage conditions at a low temperature is prevented selectively when disodium edetate is formulated in an aqueous liquid preparation of Gatifloxacin.

7. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or

imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

This 18th day of June, 2001

Katsuhiro Inada

Katsuhiro INADA